Natural History of Moderate Mitral Valve Stenosis

Diana Rinkevich MD[1], Jonathan Lessick MD PhD[2], Diab Mutlak MD[2], Walter Markiewicz MD[2] and Shimon A. Reisner MD[2]

[1]Department of Cardiology, Hillel Yaffe Medical Center, Hadera, Israel
[2]Department of Cardiology, Rambam Medical Center, Haifa, Israel
Affiliated to Technion Faculty of Medicine, Haifa, Israel

Key words: mitral stenosis progression, predictive factors, echocardiography

Abstract

Background: With the introduction of surgery and percutaneous balloon valvuloplasty for relieving severe mitral stenosis the natural history of the disease has markedly altered.

Objectives: To determine the natural history of the disease in patients with moderate mitral valve stenosis.

Methods: Demographic, clinical and echocardiographic data were evaluated in 36 patients with moderate mitral stenosis during a follow-up of 71 $\pm$ 15 months.

Results: The 36 patients comprised 32 women and 4 men with a mean age of 43.7 $\pm$ 12.2 years; 28 were Jewish and 8 were of Arab origin. During follow-up, there was a significant decrease in mitral valve area, with an increase in mean mitral valve gradient and score. Mean loss of mitral valve area was 0.04 $\pm$ 0.11 cm^2/year. No correlation was found between disease progression and age, past mitral valve commissurotomy, baseline mean gradient or mitral valve score. Larger baseline mitral valve area (P = 0.007) and Arab origin (P = 0.03) had an independent correlation to loss of mitral valve area. Fifteen patients (42%) did not demonstrate any loss in mitral valve area during the follow-up period.

Conclusions: The rate of mitral valve narrowing in patients with moderate mitral stenosis is variable and cannot be predicted by patient's age, past commissurotomy, valve score or gradient. Secondly, larger baseline mitral valve area and Arab origin showed an independent correlation to loss of mitral valve area; and finally, in many patients valve area did not change over a long observation period.

IMAJ 2003;5:15–18

Rheumatic mitral stenosis is an acquired progressive form of valvular heart disease, characterized by diffuse thickening of the mitral leaflets, fusion of the commissures and shortening and fusion of the chordae tendineae. These pathologic lesions combine to decrease the size of the mitral valve orifice, thereby restricting the flow of blood into the left ventricle [1]. When the decrease in mitral valve area becomes critical, surgical correction [2] or percutaneous balloon valvuloplasty [3] is required.

The progression of mitral stenosis is generally slow, although it varies widely among different patients. In general, in developing countries and tropical areas the disease is often rapidly progressive [4]. The natural history of untreated mitral stenosis was studied prior to the advent of techniques for relieving mitral stenosis and in patients refusing surgery [5–8]. The mortality of untreated patients with significant mitral valve stenosis was about 40% at 10 years and over 80% at 20 years, depending on the patient's clinical status and age.

More recent serial hemodynamic and Doppler echocardiographic studies enabled the estimation of annual mitral valve area loss [9,10]. These studies detected a wide dispersion of mitral valve area loss, without reaching a consensus regarding the factors that may predict disease progression.

With the introduction of surgical techniques for relieving mitral stenosis, the natural history of the disease has markedly altered. Patients with severe symptomatic mitral stenosis are referred to surgery or balloon valvuloplasty. The goal of our study was to determine the natural history of patients with a moderate degree of stenosis in order to provide them with effective follow-up [11,12].

Materials and Methods

Patient selection

During 38 months, between 1 November 1989 and 31 December 1992, definitive echocardiographic criteria of chronic rheumatic heart disease were found in 392 patients and stored in the database of the non-invasive cardiology unit at Rambam Medical Center, Haifa, Israel. Pure moderate mitral stenosis defined as a mitral valve area of 1.2–1.9 cm^2 was found in 56 patients (15%). Patients with more than mild mitral regurgitation [13] and those with aortic or tricuspid valve disease were excluded from the study.

Because of difficult follow-up and frequent associated systemic diseases that may influence prognosis, eight patients aged 70 or older at the time of the baseline echocardiographic study were excluded from follow-up. Three patients died of non-cardiac causes and nine other patients were lost or refused follow-up. The remaining 36 patients comprised the study group.

Two-dimensional and Doppler echocardiography

All studies were performed using an Acuson 128XP (Mountain View, CA, USA) or a Hewlett Packard Sonos 1000 (Andover, MA, USA) ultrasound machine equipped with 2.5 and 3.5 MHz phased-array transducers. Continuous-wave Doppler was performed with a 1.9 non-imaging transducer connected to the ultrasound machine. Two-dimensional and M-mode echo measurements were performed from the long or short parasternal view, or the subcostal view, according to the American Society of Echocardiography recommendations [14]. Pressure gradients were calculated from velocities using the Bernoulli equation modified by Holen-Hatle: $\Delta P=4V^2$.

Mitral valve area was measured with the pressure half-time method using the software package on the ultrasound machine [15]. The average values of 3–5 beats in patients with normal sinus rhythm and 5–10 beats in patients with atrial fibrillation are routinely accepted for the above measurements. Mitral valve score was evaluated using the method described by Wilkins et al. [16]. This method assigns a severity grade of 0 to 4 for each of the following characteristics of the mitral valve: mobility, subvalvular thickening, leaflets thickening, and calcification. A total echocardiographic score (0 to 16) is derived by summing the individual scores. Higher score values represent increasing degrees of morphologic disease. Systolic right ventricular (or pulmonary artery pressure) was calculated using the modified Bernoulli equation given by: PAP = 4 x (tricuspid systolic jet)^2 + 10 mmHg (estimated right arterial pressure) [17].

Follow-up

The mean follow-up period was 71 ± 15 months (range 16–93). Evaluation of functional capacity (New York Heart Association), prescription of medical therapy, and the decision to refer the patient to mitral valve surgery or percutaneous balloon mitral valvuloplasty, was performed according to usual clinical and echocardiographic criteria by the attending cardiologist at each visit. In case of intervention, the last echo study before intervention was considered as the last follow-up study.

Statistical methods

Echocardiographic data at baseline and at the last follow-up visit were compared using the two-tailed, paired, Student *t*-test. Demographic and echo data between subgroups of patients were compared using the two-tailed, non-paired, Student *t*-test. Stepwise backward multiple regression analysis was performed on the model to define which parameters could independently predict mitral valve annual area loss, using the Microsoft Excel Version 7. For the comparison of proportions, the Primer of Biostatistics Version 4 was used. Data are presented as mean ± 1SD. For all statistical tests, $P < 0.05$ was regarded as statistically significant

Results

Patients' characteristics

There were 32 women (89%) and 4 men, with a mean age at entry to the study of 43.7 ± 12.2 years (range 21–69). In 14 of the 36 patients (39%), mitral valve commissurotomy due to severe mitral stenosis was performed 4–28 years before recruitment to the study. Twenty-eight of the patients were Jewish and 8 patients were of Arab origin. Atrial fibrillation was present in 8 of the 36 patients (22%) at baseline and in 13 patients (36%) at the last follow-up visit. At baseline there were no patients in FC III. At the last follow-up visit, eight patients (22%) were in FC III. Systemic hypertension was found in five patients and diabetes mellitus in two.

Most patients (70%) were on medical therapy. Anticoagulation with warfarin was administered to 13 patients. Beta receptor blockers, calcium channel antagonists, digoxin, angiotensin-converting enzyme inhibitors and diuretics were used in 17%, 19%, 17%, 14% and 22%, respectively. No patient had clinically evident exacerbation of rheumatic activity during follow-up.

Echocardiographic and hemodynamic data

Echocardiographic characteristics of the patients at entry to the study and at last follow-up visit are presented in Table 1. During the follow-up, there was a significant decrease in mitral valve area, and increases in mean mitral valve gradient, mitral valve score and left atrial dimension.

Progression of moderate mitral stenosis

The mean rate of decline in mitral valve area was 0.04 ± 0.11 cm^2/year. Fifteen patients did not show any decrease in mitral valve area during the follow-up period. These 15 patients (termed the no progression group) were compared with the 10 patients who had annual loss of mitral valve area larger than average (0.12 ± 0.11 cm^2/year, range 0.042–0.7 cm^2/year), the "fast progression group." Demographic and echo characteristics of these two subgroups are summarized in Table 2.

Patients in the "fast progression group" had a significantly larger baseline mitral valve area. Forty percent of the "fast progression group" patients were of Arab origin compared to only 13% in the "no progression group," but this difference did not reach statistical significance. All other demographic or echo data were similar in the two subgroups.

Table 1. Echocardiographic characteristics of study patients at entry and last follow-up visit

	Entry	Last follow-up	*P*
Mitral valve area (cm^2)	1.53±0.18	1.41±0.20	0.0005
Mean gradient (mmHg)	5.9±2.0	7.0±3.1	0.004
Mitral valve score	5.1±1.7	6.3±2	0.005
Left ventricular (ED), (mm)	49.3±5.9	49.4±4.5	NS
Fractional shortening (%)	39±7	39±6	NS
Left atrium (mm)	44.3±6.1	47.5±6.2	0.0002
PA pressure (mmHg)	37±10	39±10	NS

ED = end diastole

Table 2. Demographic and echocardiographic characteristics of patients with fast progression versus patients without progression of mitral stenosis

	Fast progression (n=10)	No progression (n=15)	*P*
Age (yr)	43.8±15.5	44.8±12.6	NS
Women/Men	8/2	13/2	NS
Past commissurotomy	5 (33%)	4 (40%)	NS
Arab origin	40%	13%	NS
Follow-up time (months)	64.3±22.6	71.3±10.7	NS
Baseline MVA (cm^2)	1.7±0.17	1.41±0.20	0.0006
Baseline MG (mmHg)	5.5±1.3	6.1±1.8	NS
Baseline score	5.0±1.8	5.7±1.9	NS

PAP = pulmonary arterial pressure
FC = functional class

Baseline factors predicting mitral valve stenosis progression

By univariate analysis the following parameters were evaluated in relation to the annual loss of mitral valve (cm^2/year) and are presented in ascending order of significance: past mitral valve commissurotomy ($r = 0.11$), mean gradient ($r = 0.12$), mitral valve score ($r = 0.12$), age ($r = 0.18$), mitral valve area ($r = 0.32$, $P = 0.051$), and patient's origin (Jewish versus Arab) ($r = 0.35$, $P = 0.038$).

Since several different but interdependent parameters may have prognostic importance, we performed multivariate analysis on these variables. Only two parameters were found to have independent correlation to the annual loss of mitral valve area: the rate of progression, which was significantly greater among patients with a larger baseline mitral valve area ($P = 0.007$), and Arab origin ($P = 0.03$).

Significance of patient's origin

in the study group there were eight patients of Arab origin. These patients were significantly younger at the first follow-up visit (29.3 $\pm$ 4.6 versus 47.9 $\pm$ 10 years, $P < 0.0001$; Arab vs. Jewish origin, respectively), had significantly faster progression of the disease (0.11 $\pm$ 0.23 vs. 0.02 $\pm$ 0.02, cm^2year, $P = 0.038$) and a significantly shorter follow-up period (59.6 $\pm$ 22.8 vs. 75.9 $\pm$ 11.9, months, $P = 0.009$). There was no significant difference in baseline mitral valve area, mean gradient or mitral valve score between these two populations. Three Arab patients (38%) were referred to surgery during the follow-up period as compared to only 3 of the 28 Jewish patients (11%).

Effect of past mitral valve commissurotomy on disease progression

There was no difference in the mean age and follow-up time of the 14 patients (12 women) with past mitral valve commissurotomy compared to the other 22 patients. These 14 patients had a significantly larger baseline mitral valve area compared to the 22 patients who did not undergo the surgical procedure (1.65 $\pm$ 0.17 vs. 1.45 $\pm$ 0.19 cm^2 respectively, $P = 0.002$). This advantage was maintained during follow-up, with mean mitral valve area of 1.52 $\pm$ 0.16 vs. 1.33 $\pm$ 0.15 cm^2, respectively, $P = 0.002$, in the last echo study. Annual mitral valve area loss in the two groups was similar (0.13 $\pm$ 0.18 vs. 0.13 $\pm$ 0.20 cm^2/year, receptively, P not significant).

Discussion

Progression of moderate mitral valve stenosis

Rheumatic mitral valve stenosis is a slowly progressive disease. In our study we found a slow mean rate of annual area loss of 0.04 cm^2/year with a large standard deviation of about 0.11 cm^2/year. Actually, in 15 patients (42%) no decrease in annual area loss was detected, whereas 10 of the 36 patients (28%) had evident progression of the disease during a similar follow-up time [Table 2].

Sagie et al. [9] studied 103 patients (mean age 61 years; 74% female) with serial two-dimensional and Doppler echocardiography. The follow-up period was 3.3 $\pm$ 2.0 years. The study group included patients with a wide range of baseline mitral valve (mild to severe stenosis), as well as patients with combined mitral and aortic valve disease. During follow-up, mitral valve area decreased at a mean rate of 0.09 cm^2/year. In 28 patients there was no decrease and in another 40 there was a slow progression of mitral valve narrowing. Similar to our results, though with a weak correlation by multivariate analysis, the rate of progression was significantly greater among patients with a larger initial mitral valve area. No other variables evaluated in the study could predict disease progression in individual patients. Mean annual mitral valve area loss in the patients with moderate stenosis was very close to our study results (0.06 cm^2/year).

Gordon et al. [10] studied 50 patients with rheumatic mitral stenosis using serial two-dimensional and Doppler echo during 7–74 months (mean 39). The mean decline in valve area was 0.09 cm^2/year with a very large standard deviation of 0.21 cm^2/year. Contrary to our findings, patients with an echocardiographic score $\geqslant$ 8 in Gordon's study had a more progressive course. In addition, patients with a more progressive course had a significantly greater initial mean gradient ($P = 0.01$), peak gradient ($P = 0.007$) and total echo score ($P = 0.0008$). Initial valve area did not correlate with the rate of stenosis progression. Our patients were younger and only three patients had a baseline mitral valve score $\geqslant$ 8.

Ethnic origin as a predictor of progression of mitral valve stenosis

A meta-analysis [18] showed a significant negative association with HLA-DR5 and a positive association between HLA-DR4 and HLA-DR7 and rheumatic heart disease, suggesting a link between susceptibility to rheumatic heart disease and genetics. A study on patients of Arab origin [19] reported positive HLA-DR4 association and rheumatic heart disease.

There is a persistent decline in the incidence of rheumatic fever in Israel. Acute rheumatic fever remains more common in the non-Jewish than in the Jewish population and in children from relatively overcrowded and deprived homes [20–22]. We have no data regarding appropriate antibiotic prophylaxis throughout the follow-up interval, no serologic evidence of recurrent rheumatic activity and no HLA data. Therefore, the possibility that disease progression in our patients was related to asymptomatic recurrence of rheumatic fever rather than to genetic factors cannot be excluded.

Limitations

We present a long follow-up on a small group of patients from a single outpatient clinic and echocardiographic laboratory. Some patients had previous mitral valve commissurotomy. Data were collected from patients' clinical files and readers were not blinded to clinical data or sequence of examinations. The observation of faster progression of mitral stenosis in the Arab population, though statistically significant, is based on a small number of patients and should be considered as preliminary. The socioeconomic status of our patients, serologic evidence of recurrent rheumatic activity, and HLA data were not evaluated in the current study. Exacerbation of rheumatic activity was only clinically evaluated and subclinical events might have been missed.

Conclusions

The rate of mitral valve narrowing in individual patients with moderate mitral valve stenosis is variable and cannot be predicted by patient's age, past mitral valve commissurotomy, mitral valve score or transmitral gradient. Despite the weak correlation by multivariate analysis, the rate of progression is significantly greater among patients with a larger initial mitral valve area.

Arab origin was independently correlated to loss of mitral valve area. This observation was based on a small number of patients and needs to be evaluated in a controlled prospective study.

In many patients with moderate mitral stenosis, mitral valve area did not undergo any major changes over a relatively long observation period, reflecting the substantial stability of the valve disease process. These patients may be identified after the second or third follow-up visit. Yearly echocardiographic examination in these patients appears to be unjustified unless clinical progression is noted.

References

1. Dalen JE. Mitral stenosis. In: Dalen JE, Alpert JS, eds. Valvular Heart Disease. Boston: Little, Brown 1987:49–110.
2. Heger JJ, Wann LS, Weyman AE, Dillon JC, Feigenbaum H. Long-term changes in mitral valve area after successful mitral commissurotomy. *Circulation* 1979;59:443–8.
3. Palacios I, Block PC, Brandi S, et al. Percutaneous balloon valvuloplasty for patients with severe mitral stenosis. *Circulation* 1987;75:778–84.
4. Chopra P, Bhatia ML. Chronic rheumatic heart disease in India: a reappraisal of pathologic changes. *J Heart Valve Dis* 1992;1(1):92–101.
5. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery: ten- and twenty-year perspectives. *Ann Intern Med* 1960;52:741–9.
6. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br Heart J* 1962;24:349–57.
7. Rapaport E. Natural history of aortic and mitral value disease. *Am J Cardiol* 1975;35:221–7.
8. Horstkotte D, Niehues R, Strauer BE. Pathomorphological aspects, aetiology and natural history of acquired mitral valve stenosis. *Eur Heart J* 1991;12(Suppl B):55–60.
9. Sagie A, Freitas N, Padial LR, et al. Doppler echocardiographic assessment of long-term progression of mitral stenosis in 103 patients: valve area and right heart disease. *J Am Coll Cardiol* 1996;28(2):472–9.
10. Gordon SPF, Douglas PS, Come PC, Manning WJ. Two-dimensional and Doppler echocardiographic determinants of the natural history of mitral valve narrowing in patients with rheumatic mitral stenosis: implications for follow-up. *J Am Coll Cardiol* 1992;19:968–73.
11. Faletra F, De Chiara F, Crivellaro W, Mantero A, Corno R, Brusoni B. Echocardiographic follow-up in patients with mild to moderate mitral stenosis: is a yearly examination justified? *Am J Cardiol* 1996;78 (12):1450–2.
12. Bonow RO, Carabello B, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation* 1998;98 (18):1949–84.
13. Abbasi AS, Allen MW, DiCristofaro P, Ungar I. Detection and estimation of the degree of mitral regurgitation by range-gated pulsed Doppler echocardiography. *Circulation* 1980;61:143–7.
14. Feigenbaum H. Echocardiography. 4th edn. Philadelphia: Lea & Febiger, 1986:625.
15. Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation* 1979; 60:1096–104.
16. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and mechanism of dilatation. *Br Heart J* 1988;60:299–308.
17. Berger M, Haimowitz A, Van Tosh P, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1985;6:359–65.
18. Carlquist J, Ward R, Meyer K, Husebye D, Feolo M, Anderson JL. Immune response factors in rheumatic heart disease: meta-analysis of HLA-DR associations and evaluation of additional class II alleles. *J Am Coll Cardiol* 1995;26:452–7.
19. Rajapakse CN, Halim K, Al-Orainey I, Al-Nozha M, Al-Aska AK. A genetic marker for rheumatic heart disease. *Br Heart J* 1987;58:659–62.
20. Halfon ST. Epidemiologic aspects of rheumatic fever and rheumatic heart disease in Israel. *Isr J Med Sci* 1979;15:999–1002.
21. Yarrow A, Slater PE. The decline of acute rheumatic fever in Israel. *Public Health Rev* 1990;18:239–49.
22. Eshel G, Lahat E, Azizi E, Gross B, Aladjem M. Chorea as a manifestation of rheumatic fever – a 30-year survey (1960-1990). *Eur J Pediatr* 1993;152:645–6.

Correspondence: Dr. S.A. Reisner, Dept. of Cardiology, Rambam Medical Center, Haifa 31096, Israel.
Phone: (972-4) 854-2342
Fax: (972-4) 854-3507
email: rshimon@tx.technion.ac.il